## REMARKS

Claim 1 has been amended to include elements from previous claims 2 and 3. Claims 2, 3 have been rendered redundant by this amendment and have been cancelled. Claim 9 has been cancelled too. Claims referring to M291 or visilizumab have been amended to define antibodies by reference to sequences rather than these names. Support is provided by US 5,834,597 (particularly the sequence listing and col. 18, line 64 indicating humanized M291 with a light chain constant region), which is incorporated by reference. Support for new claims 26 and 29 is provided at e.g., p. 15, lines 10-14. Amendments should not be construed as acquiescence in any ground of rejection. Lack of comment on any point mentioned by the Examiner should not be viewed as agreement. Applicant responds to the office action using the paragraph numbering of the office action.

4. A sequence listing is provided. The sequence listing contains SEQ ID NOS. 2, 4, 6, 8 and 9 of US 5,834,597 referring to sequences of the M291 antibody and humanized versions thereof. These SEQ ID NOS. are renumbered as SEQ ID NOS. 4, 5, 1, 2 and 3 respectively in the present case for conformity with the SEQ ID NOS. already used in the specification. These sequences are incorporated by reference into the present specification (see, e.g., p. 11, line 25). This amendment is accompanied by a computer disk containing the Sequence Listing in computer readable form, and a paper copy of the Sequence Listing that has been prepared from the computer disk. The information contained in the computer disk was prepared using the software program "PatentIn" and is identical to the paper copy.

7. Applicants agree to designate trademarks as such. It is noted, however, that the term visilizumab is not a trademark but an International Non-Proprietary Name. The trademark for the same antibody is Nuvion®, and Nuvion® is designated as a registered mark.

8. The abbreviations have been spelled out as requested.

9-10. A. Regarding the term "visilizumab," applicant notes that such is not an arbitrary name, but rather an International Non-Proprietary Name assigned by the World Health Organization to facilitate the identification of pharmaceutical substances. Nevertheless, the terms M291 and visilizumab are no longer used in the claims. The previous designation of humanized M291 is now defined by reference to a humanized version of a mouse antibody having the variable regions of SEQ ID NOS. 4 and 5 corresponding to the variable regions of M291. The constant regions of mouse M291 are irrelevant to humanization because a humanized antibody does not retain the mouse constant regions of the starting mouse antibody. Thus, the current terminology defines the same class of antibody without referring to M291 per se. Likewise, visilizumab has been defined in other words by reference to the sequence of its variable regions, its heavy chain constant region (a human IgG2 mutant) and a kappa light chain constant region (see, e.g., col. 18, line 64 of US 5,834,597). Such description is commensurate with the description in US 5, 834,597, which is incorporated by reference.

B. Claim 9 has been cancelled mooting the rejection.

11-12. Issues with respect to deposit or reproducibility of M291 or visilizumab are moot in that these terms are no longer used in the claims as discussed above.

13. Claim 18 has been canceled without prejudice.

14-15. Claims 1, 3-17 and 19-25 stand rejected as allegedly anticipated by Tso. This rejection is moot in view of the incorporation of the element of claim 2 into claim 1.

16-17. Claims 1-26 stand rejected as unpatentable over Tso in view of Lobb, Rutgeerts, Banerjee, and Strom. Tso is alleged to teach humanized anti-CD3 antibodies and their use in treating inflammatory bowel disease. Lobb is alleged to teach that inflammatory bowel disease includes ulcerative colitis and Crohn's disease. Rutgeerts is alleged to teach alternative treatments of patients who are refractory to corticosteroids, such as an anti-TNF-alpha antibody.

Banerjee is alleged to each administration of methylprednisolone together with TNF-alpha antibody. Strom is alleged to teach known advantages of using a multi-tiered approach to immunosuppresive therapy. The Examiner alleges that one would have been motivated to treat patients refractory to corticosteroids with anti-CD3 antibodies because Rugeerts teaches that patients with refractory inflammatory bowled disease are "frustrated" because alternative treatments carry toxicity and neoplasia risks and so newer options such as anti-TNF-alpha are desirable. The Examiner also alleges that one would be motivated to combine anti-CD3 with a corticosteroid in the hope of achieving synergistic effects that overcome steroid resistance.

It is respectfully submitted that the cited art did not suggest or provide a reasonable expectation of success that anti-CD3 antibodies could be successfully used in treating patients with severe steroid-refractory ulcerative colitis. The Tso reference mentions inflammatory bowel disease only as one of a list of many diseases, and does not specifically refer to ulcerative colitis, much less severe steroid refractory ulcerative colitis.

Moreover, the expectation of success or lack thereof should be viewed in the context that the population to be treated would have already failed conventional steroid therapy and have had a poor outlook. As discussed in the specification (see p. 2), the only alternatives for such patients were cyclosporine and investigational drugs. Cyclosporine is highly toxic requiring stays of 7-14 days in a hospital, and largely unsuccessful in that 70% of patients so treated require surgery associated with significant morbidity within a year (specification at p. 2, second paragraph). The investigation drugs are of undetermined efficacy. The limited options for patients at the priority date of the invention suggest that finding a successful treatment was not a routine matter.

This state of the art is in fact confirmed by the Rutgeerts reference, which as the Examiner has noted, refers to the "frustrated" state of existing patients, and the severe side effects of existing treatments (for example cyclosporin treatment resulted in long term survival without colectomy in only 35.5% of patients, see p. 913, paragraph bridging cols. 1 and 2). The reference does mention that various treatments with cytokines and anti-cytokines have been developed for clinical experimental use of which anti-TNF is one (p. 914, first column, paragraph 4). However, the reference also refers to many other possibilities under investigation

(p. 914, first column, paragraph 5). Moreover, the immune system is complex and antibodies other than those listed by Rutgeerts are available to suppress many of its components and processes. The NIH website (www.clinicaltrials.gov/ct/gui/action/SearchAction?term=Ulcerative+Colitis) alone indicates that 72 clinical trials are now in progress with various agents to attempt to treat ulcerative colitis. It is also well known that clinical trials are expensive and time consuming to conduct and most do not result in an approvable product.

In these circumstances, it is respectfully submitted that the art discloses no more than a frustration with existing treatments, and that much effort was being devoted to find improved treatments. However, the skilled person was still left with many possible avenues that could have been explored not knowing which would be successful. Given the expense and uncertain outcome of conducting clinical trials, the difficulty of treating a condition that by definition is resistant to treatment with steroids, the skilled person would not have provided a reasonable expectation of success that the presently claimed methods would have been successful.

Notwithstanding these difficulties and uncertainties, the present application provides data showing dramatic and durable effects from administration of the claimed antibodies to patients with severe steroid refractory ulcerative colitis. In a first trial of eight patients (specification at pp. 44-46), seven of the eight achieved remission and the other showed detectable benefits. The patients were released from hospital with a mean stay of only 3 days compared with 7-14 days for cyclosporine A treatment or colectomy. In a second trial of 23 patients with severe steroid refractory ulcerative colitis (specification at pp. 47-48), after receiving only two doses on consecutive days, 19 of 23 patients showed long-term improvement in condition for up to 16 months post treatment with no serious adverse events. Thus, the present claims represent an unexpected solution to the serious problem hitherto faced by patients with severe steroid refractory ulcerative colitis.

It is respectfully submitted that claims 23-24 are inventive on independent grounds in that these claims recite effective dosages that are much lower than dosages used with most other antibody therapies. Although the claimed dosages may overlap with the lower end of ranges discussed by Tso (when the Tso doses are converted to mg/kg), Tso's ranges do not

provide specific direction for treating severe steroid resistant ulcerative colitis. Tso's dosage ranges are broad and not proposed specifically for treating ulcerative colitis, much less severe steroid refractory ulcerative colitis. Moreover, Tso was written at a time when very few antibodies had been approved for clinical use. Subsequent experience has been that dosages toward the higher end or above the ranges proposed by Tso are used. For example, dosages used with other antibody treatments are shown in the Table below. Most dosages are in the *mg*/kg range. By contrast, the clinical trials discussed above show that ulcerative colitis can be treated using dosages of only 10 or 15 *micro*grams per kg of the claimed antibodies. The use of low dosages is advantageous in avoiding side effects, reducing costs of manufacture and formulation of a drug. In light of experience with other antibodies, the low effective dosages of the claimed antibodies in treating severe steroid refractory ulcerative colitis represent an unexpected result.

| Antibody | Manufacturer | Dosage | Calculated Dosage for 75 kg patient | Reference |
|---|---|---|---|---|
| **Orthoclone OKT3 (muromonab-CD3)** | J & J -Ortho Biotech | 1 mg/kg | 75 mg/dose | Orthoclone OKT3 package Insert, from product website http://www.orthobiotech.com/pdfs/okt3.pdf#search='orthoclone%20OKT3' |
| **Reopro (abciximab)** | Centocor-Lilly | 0.25 mg/kg | 18.75 mg/dose | Lilly product website: http://www.reopro.com/news_information/faqs.jsp |
| **Rituxan (rituximab)** | Idec-Genentech | | Dosage differs by therapy: For relapsed or refractory, low grade or follicular, CD20-positive, B-cell, Non-Hodgkin's Lymphoma: 375 mg infusion once weekly for 4-8 doses Retreatment | Rituxan package Insert, from product website http://www.gene.com/gene/products/information/pdf/rituxan-prescribing.pdf |

| Antibody | Manufacturer | Dosage | Calculated Dosage for 75 kg patient | Reference |
|---|---|---|---|---|
| | | | therapy:<br><br>375 mg infusion once weekly for 4-8 doses<br><br>For treatment of diffuse large B-cell NHL: 375 mg infusion per cycle of chemotherapy up to 8 infusions<br><br>For treatment of rheumatoid arthritis:<br><br>2 1000 mg infusions separated by 2 weeks<br><br>As component of Zevalin® therapeutic regimen:<br><br>250 mg/ml should be infused within 4 hours prior to administration of Yttrium-90-Zevalin | |
| **Zenapax**<br><br>**(daclizumab)** | Roche | 1 mg/kg | 75 mg/dose | Zenapax product information, from product website:<br><br>http://www.rocheusa.com/products/zenapax/pi.pdf |
| **Simulect**<br><br>**(basiliximab)** | Novartis | 2 doses, 20 mg/dose<br><br>(doses administered prior to and subsequent to transplant) | 40 mg in 2 doses | Simulect product information, from product website:<br><br>http://www.pharma.us.novartis.com/product/pi/pdf/simulect.pdf#search='simulect' |

| Antibody | Manufacturer | Dosage | Calculated Dosage for 75 kg patient | Reference |
|---|---|---|---|---|
| **Synagis** (palivizumab) | MedImmune | 15 mg/kg | 1125 mg/dose | Synagis product information, from product website: http://www.synagis.com/hcp/pdf/synagis_pi.pdf |
| **Remicade** (infliximab) | Centocor | Dosage differs by therapy: Rheumatoid arthritis: 3 mg/kg Crohn's Disease: 5 mg/kg | Rheumatoid arthritis: 225 mg/dose Crohn's Disease: 375 mg/dose | Remicade product information, FDA website http://www.fda.gov/cder/foi/label/2000/inflcen111099lb.pd |
| **Herceptin** (trastuzumab) | Genentech | 4 mg/kg | 300 mg/dose | Herceptin product information, from product website: http://www.gene.com/gene/products/information/oncology/herceptin/insert.jsp#administration |
| **Mylotarg** (gemtuzumab ozogamicin) | Wyeth | 9 mg/m$^2$ 0.1mg/kg | 7.5 mg/dose | Mylotarg product information, from product website: http://www.wyeth.com/content/ShowLabeling.asp?id=119 |
| **Campath** (alemtuzumab) | Millenium-ILEX | | 30 mg/day (maintenance dose, administered 3X/week) | Campath package Insert, from product website http://www.berlex.com/html/products/pi/Campath_PI.pdf |
| **Zevalin** (radioactive) | Biogen Idec | | 2 parts: 1.6 mg/dose | Zevalin product information, from product website http://www.zevalin.com/pdf/zevalin_pi.pdf |
| **Humira** (adalimumab) | Abbott | 40 mg every other week | 40 mg every other week | Humira product information, from product website http://www.rxabbott.com/pdf/humira.pdf |
| **Xolair** (omalizumab) | Genentech | | 150-300 mg every 2-4 weeks | Xolair product information, from product website http://www.xolair.com/patient/prescribing_info.jsp |
| **Bexxar** (Tositumomab) | Corixam-GSK | | 4 components in 2 discrete steps: Dosimetric step: | Bexxar product information, from product website http://us.gsk.com/products/assets/us_bexxar.pdf |

| Antibody | Manufacturer | Dosage | Calculated Dosage for 75 kg patient | Reference |
|---|---|---|---|---|
| | | | 450 mg + 35 mg<br>$I^{131}$ Tostiumomab<br>Therapeutic step:<br>450 mg + 35 mg<br>$I^{131}$ Tostiumomab | |
| **Raptiva**<br>**(efalizumab)** | Genentech | 0.7 mg/kg SC conditioning dose followed by weekly SC doses of 1 mg/kg | Conditioning dose:<br>52.5 mg<br>Therapeutic dose:<br>75 mg | Raptiva product information, from product website<br>http://www.gene.com/gene/common/inc/pi/raptiva.jsp |
| **Erbitux**<br>**(cetuximab)** | Imclone Systems | 10.04 mg/kg | 753 mg initial loading dose<br>470 mg maintenance dose | Erbitux product information, from product website<br>http://www.bms.com/cgi-bin/anybin.pl?sql=select%20PPI%20from%20TB_PRODUCT_PPI%20where%20PPI_SEQ=106&key=PPI |
| **Avastin**<br>**(bevacizumab)** | Genentech | 5 mg/kg (when administered with bolus-IFL) or 10 mg/kg (when used w/ FOLFOX4) every 14 days | 375 or 750 mg every 2 weeks | Avastin product information, from product website<br>http://www.gene.com/gene/products/information/oncology/avastin/insert.jsp#administration |
| **Tysabri**<br>**(natalizumab)** | Biogen Idec | | 300 mg every 4 weeks | Tysabri product information, from product website<br>http://www.tysabri.com/TYSABRI-pi.pdf |

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

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